REMARKS

Claims 1-17 and 28-37 were previously pending and rejected in this application. Claims 1-9, 12, 14, 28, 32, 34, and 36 are amended, herein. Applicant hereby requests cancellation of Claims 29, 30, 31, 33, 35 and 37. Thus, after entry of this amendment claims 1-17, 28, 32, 34 and 36 will be pending in this application.

Applicant believes that the claims as amended are clearly distinguishable over all of the references of record. Reconsideration of claims 1-17, 28, 32, 34 and 36 in light of the amendments and arguments below is respectfully requested.

NO NEW MATTER IS INTRODUCED BY THE AMENDMENTS TO THE CLAIMS.

No new matter is presented by way of the amendments to any of claims 1-9, 14, 28, 32, 34 and 36. Literal support for the amendments to claim 1, and to claims 2-7 dependent therefrom is found, e.g., in Example 9 in the paragraph bridging pages 47-48, in SEQ ID NO:14 and in FIGURE 2, and in the subsequent Examples. Literal support for the amendments to claims 8, 9, 12, 14, 28, 32, 34 and 36 is found in claim 1 as originally filed (and in claim 1 as currently amended).

Claims 1-7 are amended to clarify certain aspects of the subject matter currently being pursued in this application. More particularly, claims 1-7 are amended to indicate that the signal sequence is an engineered Japanese Encephalitis Virus (JEV) signal sequence, and that the immunogenic flavivirus antigen is selected from a virus other than JEV. Claims 8, 9, 12, 14, 28, 32, 34 and 36 are amended solely to render the language used to refer to the subject "antigen" consistent with of that of the antecedent basis for an "immunogenic flavivirus antigen" in claim 1. These amendments are presented in order to expedite prosecution, and nothing in these amendments is to be construed to indicate agreement with any rejection or argument of record. Applicant is entitled to entry and consideration of these amendments in light of the accompanying Request for Continued Examination under 37 CFR 1.114.

RESUBMISSION OF REFERENCES CITED IN PREVIOUSLY SUBMITTED IDS

The Office Action states that the references accompanying the information disclosure statement (IDS) filed April 11, 2003, and received by the Patent Office on April 14, 2003, were not considered because copies of the submitted patents and publications were not entered into the electronic file wrapper for this application. Upon closer inspection of the filed documents, it appears that the form 1449 originally submitted with the references was inadvertently copied from a related application. Applicant is therefore submitting herewith a newly printed copy of the correct form 1449, along with the references previously submitted on April 11, 2003, in this application.

Additionally, Applicant notes that there is no indication that information disclosure statements filed July 27, 2001, and February 15, 2002, have been considered. Applicant respectfully requests that the Examiner return an initialed copy of the forms 1449 submitted on July 27, 2001, and February 15, 2002 indicating that the references cited therein have been considered. In the event that copies of the references cited in the July 27, 2001, and February 15, 2002, information disclosure statements are not available in the file, Applicant would be happy to provide copies of the previously submitted references. Accordingly, the Examiner is invited to contact the undersigned at (503) 595-3815 to request delivery of copies of the references cited in the July 27, 2001, and February 15, 2002 information disclosure statements.

THE CLAIMS ARE NOT OBVIOUS WITH RESPECT TO YASUI, KOCHEL AND/OR IVY.

Claims 1-17 and 28-37 were rejected under 35 U.S.C. §103(a), as allegedly unpatentable over Yasui *et al.* (1990) in view of Kochel *et al.* (2002) and Ivy *et al.* (2000). Applicant traverses this rejection, and requests that it be withdrawn in light of the amendments and remarks presented below.

At least three basic requirements must be met to establish a *prima facie* case of obviousness. First, the Office must show how the prior art reference must contain all of the limitations of the claims. M.P.E.P. § 2143.03. Second, the Office must establish that there was a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, the Office must demonstrate that there was a reasonable expectation

of success for achieving the invention in the prior art. M.P.E.P. § 2143.02. The teaching or suggestion to combine and the expectation of success must both be found in the prior art and not based on an Applicant's disclosure. M.P.E.P. § 2142.

The prior art does not teach all of the limitations of the claimed invention.

In light of the amendments to the claims, Applicant believes that the grounds for rejection are rendered moot. None of the cited references (or any other reference of record), alone or in any combination, disclose all of the elements of the amended claims. Claim 1 is directed to a nucleic acid that includes a single transcription unit with "an engineered Japanese Encephalitis Virus (JEV) signal sequence and an immunogenic flavivirus antigen of a flavivirus other than JEV..." None of the cited references teaches or suggests a single transcription unit with an "engineered JEV signal sequence."

For example, Yasui et al. (Southeast Asian J. Trop. Med. Public Health, 21(4):663-669, 1990) is cited for teaching that PrM and E proteins include signal sequences, which are required for expression. At no point does Yasui suggest that any signal sequence can be used other than that of the wild type JEV for the M and E antigens to be expressed. Accordingly, Yasui teaches only that wild type signal sequences are important for expression of the corresponding M and E antigens. Furthermore, as admitted in the Office Action, Yasui does not teach using any signal sequence with M or E antigens from a virus other than JEV. Thus, Yasui does not teach the elements of Claim 1, or any claims dependent therefrom.

Kochel (USPN 6,455,509) is cited for teaching "preparation of nucleic acid dengue virus vaccines comprising a nucleic acid encoding the prM signal sequence and the envelope protein." It is further alleged in the Office action that "[t]hese genes may be from the same isolate or different isolates." On the contrary, Kochel describes nucleic acids in which the signal sequence is derived from the same Dengue serotype virus as the M and E antigens. To produce a vaccine capable of conferring protection to different serotypes of virus, Kochel teaches combining up to four different, separate, nucleic acids. Each of the different nucleic acids includes a signal sequence and antigen from a single serotype of Dengue virus. Applicant is unable to find any

statement in Kochel that suggests a single transcription unit with the signal sequence from a first serotype of Dengue virus and the antigen of a second serotype of Dengue virus. More importantly with respect to the amended claims, Kochel does not disclose a transcription unit with an engineered JEV signal sequence in combination with an antigen of Dengue (or any other) virus. Indeed, as acknowledged in the Office Action, there is no reference whatsoever to Japanese Encephalitis Virus, or JEV, signal sequences. Thus, Kochel cannot reasonably be interpreted as teaching the elements of the claims.

Ivy (USPN 6,136,561) is cited for teaching "preparation of nucleic acid constructs comprising a first nucleotide sequence encoding a signal sequence and a second nucleotide sequence encoding the E antigen of any given flavivirus (*e.g.*, dengue, JEV, TBE, YFV, WNV, or SEV). The signal sequence may consist of either the $htPA_L$ leader sequence or the prM leader sequence."

To the extent that Ivy is held to render the amended claims obvious, Applicant respectfully traverses. Ivy describes a construct encoding 60% or 80% envelope (E) protein from a flavivirus that can be expressed and secreted using one of very few specific leader sequences selected to give sufficient expression of a truncated E protein in cultured cells. Thus, for example, Ivy teaches a transcription unit with a yeast α-mating factor prepropeptide leader sequence ($preproMF\alpha_L$), the invertase or acid phosphatase leader of *S. cerevisiae*, or the glucoamylase of *C. albicans* or *A. niger* for expressing a flavivirus E antigen in yeast cells. Similarly, Ivy teaches a transcription unit with the human tissue plasminogen activator secretion signal sequences (tPA_L) or the bovine chymosin prepropeptide secretion leader for expression of a truncated E antigen in Drosophila cells. Ivy also states that antigens can be "secreted from the **homologous** premembrane (prM) leader." Thus, the only flavivirus signal sequence that is suggested or taught by Ivy is the signal sequence from the same virus as that from which the E protein-encoding sequence originates. Nowhere does Ivy describe using a signal sequence (such as the prM leader) from a different flavivirus than the one that provides the portion of E protein encoded by the construct. In particular, Ivy does not disclose or suggest the use of an engineered JEV signal sequence (or any other engineered signal sequence) in combination with a flavivirus

antigen (such as the E protein) of another flavivirus. Accordingly, Ivy cannot be interpreted as disclosing the claimed invention.

In conclusion, none of the cited references, whether considered singly or in any combination, teaches or suggests an engineered JEV signal sequence. Thus, the cited references do not teach all of the elements of the claims as amended and the rejection must be withdrawn.

There is no motivation in the cited references to produce a transcription unit including an engineered JEV signal sequence and an immunogenic antigen from another flavivirus.

As discussed above, the cited references do not teach the elements of the claims. For example, none of the cited references discloses or suggests an engineered JEV signal sequence. In the absence of such a disclosure, none of the cited references can reasonably be interpreted as providing the motivation or suggestion to combine an engineered JEV signal sequence with any other elements of the claims.

No reasonable expectation of success existed for making a transcription unit with an engineered JEV signal sequence in combination with an antigen of another flavivirus.

As previously discussed, the cited references do not provide any suggestion of using an engineered JEV signal sequence. In the absence of any disclosure of an engineered JEV signal sequence, there can be no reasonable expectation that combining such an engineered signal sequence with any other teaching would provide any desirable result, including the disclosed result of obtaining protective immunity to a flavivirus upon administration to a subject of the claimed nucleic acid. Accordingly, none of the prior art references, singly or in combination, can logically be read to suggest that providing a nucleic acid with a single transcription unit including an engineered JEV signal sequence and an antigen of a flavivirus other than JEV would with reasonable likelihood of success provide an effective vaccine against a flavivirus infection. Only impermissible hindsight based on Applicant's disclosure of an engineered JEV signal sequence provides any expectation that a single transcription unit including an engineered JEV signal sequence and an immunogenic flavivirus antigen from a flavivirus other than JEV will meet with success.

In light of the preceding remarks, Applicant respectfully submits that the elements of a *prima facie* case of obviousness with respect to the amended claims are not satisfied by the cited references-Yasui, Kochel and Ivy-in any combination. Therefore, Applicant requests that the rejection of claims 1-17, 28, 32, 34 and 36 be withdrawn.

CONCLUSION

It is respectfully submitted that the pending claims are in condition for allowance. If any issues remain, the Examiner is once again requested to contact the undersigned attorney prior to issuance of the next Office action, in order to arrange a telephonic interview. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request. It is believed that a brief discussion of the merits of the present application may expedite prosecution, thus, an interview is appropriate under MPEP 713.09. Applicant submits the foregoing Amendment so that the Examiner may fully evaluate Applicant's position, thereby enabling any such interview to be more focused.

Respectfully submitted,

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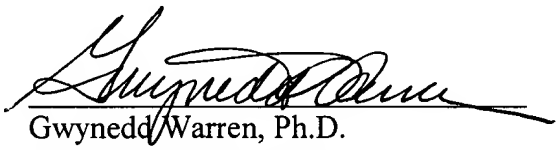
By 
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